

and

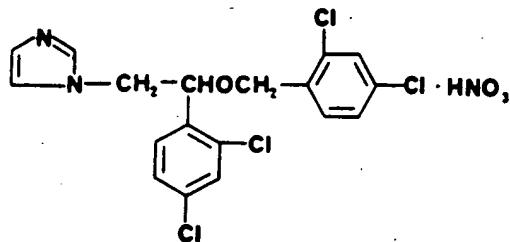
(b) zinc oxide;

wherein the miconazole nitrate and zinc oxide are present in a ratio of from about [1:40] 1:60 to about [1:1900] 1:333.

Cancel Claims 2 and 3 without prejudice.

35. (amended) A method for treating [acute inflammatory skin conditions] diaper rash comprising applying to the affected skin area a composition containing an antimicrobially effective amount of

(a) miconazole nitrate of the formula



and

(b) zinc oxide;

wherein the miconazole nitrate and zinc oxide are present in a ratio of from about [1:40] 1:60 to about [1:1900] 1:333.

#### REMARKS

Applicants wish to thank Mr. Lipovsky, the Examiner in charge of this application, for the courtesies extended to their attorney during a personal interview conducted on December 3, 1985. Many of the helpful comments and suggestions of the Examiner have been incorporated herein.

Claims 1, 4, 5 and 6 are in the case.

Claims 2 and 3 have been cancelled without prejudice.

Claims 1 and 5 were amended to reflect a ratio of miconazole nitrate to zinc oxide of from about 1:60 to 1:333. Claim 5 was also amended to reflect that the treatment is for diaper rash. It is respectfully contended that the claims as amended satisfy all of the requirements under 35 U.S.C. 112.

Claims 1-6 were rejected under 35 U.S.C. 103 as being unpatentable over Schmidt-Ruppin et al. with the contention that said reference teaches "the use of topical creams and ointments containing zinc oxide . . . which may additionally contain biologically active substances including Miconazole . . . The determination of both optimum proportions and target use are matters of obvious alternative to one with skill in the art".

The Schmidt-Ruppin et al. reference discloses a method of treating herpes infections by administering anthracene-type compounds and compositions containing same. These anthracene compounds act upon the central nervous system, and it is alleged thereby combat herpes infections. In column 7, line 43 of the reference, it indicates that pharmaceutical preparations containing these anthracene actives for topical use can be in the form of creams, ointments, gels, vaginal ovula, pastes, foams, tinctures and solutions; and in column 8, line 30 et seq.. it further indicates that pastes are creams and ointments having secretion absorbing powder constituents such as metal oxides, including zinc oxide. It also states that biologically active substances including miconazole can be added to these compositions.

Applicants respectfully contend that the teachings and disclosures of the Schmidt-Ruppin et al. reference would neither teach nor suggest to one skilled in the art the present invention. To contend that from the teaching of utilizing anthracene-type actives to act upon the central nervous system one skilled in the art would arrive at the present invention is not reasonable. To obtain Applicants' compositions from this reference, one would have to formulate the composition containing the anthracene compound in a cream form utilizing zinc oxide and add thereto miconazole and then delete the anthracene active and adjust the ratios of the remaining components. Such is clearly not obvious from the teachings of Schmidt-Ruppin et al.

The compositions of the present invention are limited to skin care compositions containing miconazole nitrate and zinc oxide in specific ratios which exhibit synergistic interaction. There is no intent whatsoever of including systemically active compounds such as the anthracene compounds disclosed in the reference, and the Examiner's reliance on this reference is considered inappropriate in view of the teachings therein.

The Office Action further contends that the ". . . showing is noted but it is not deemed to be persuasive since the proportional ratios exhibiting synergism are not commensurate with the scope of the claims."

Support for Applicants' claimed compositions with specific ratios of miconazole nitrate to zinc oxide can be found in the specification and examples. Table I on page 12 of the specification shows synergistic activity for ratios of miconazole nitrate to zinc oxide against Staphylococcus aureus

of 1:110 to 1:333 and above. In Table II, synergistic activity is shown for ratios of about 1:40 to 1:333 and above. No additional data was deemed necessary to be collected for ratios above about 1:333 since 100% inhibition is recorded. Any differences found in the results recorded in these two tables are within the normal experimental fluctuation that one finds in two-fold serial dilution experiments.

Table III on page 14 of the specification shows synergistic activities for ratios of miconazole nitrate to zinc oxide against Candida albicans of 1:240 and above and Table IV on page 15 shows synergistic activity for ratios of miconazole nitrate to zinc oxide against Candida albicans of 1:120 and above. Once again, any variations in the data reported in these two tables are within the normal experimental fluctuation that one finds in two-fold serial dilution experiments.

Synergistic efficacy of the combinations of miconazole nitrate to zinc oxide in a ratio of 1:60 against Candida albicans are shown in Example VI on pages 9 and 10 of the specification. This is a recognized in vivo test procedure and involves both microbiological measurements and clinical measurements. This procedure results in microbiological measurements from the cultures obtained by a standard detergent scrub method and clinical measurements taken by observations at various time periods. The results of these testing procedures show a statistically significant synergistic effect for the combination of miconazole nitrate and zinc oxide in a ratio of about 1:60 against Candida albicans.

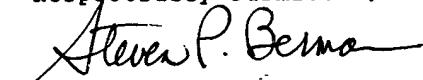
This in vivo procedure is explained in more detail in the Declarations Under Rule 132 of Dr. Bruce Semple and Dr. James J. Leyden submitted herewith. Dr. Semple, who is Vice-President - Scientific Affairs, Johnson & Johnson Baby Products, authorized this test procedure to be conducted at the Ivy Research Laboratories under the direction of Dr. Leyden.

Dr. Leyden is a foremost world authority in the field of investigative clinical dermatology as is readily evident from the background information in his Declaration. The test procedures carried out by Dr. Leyden, as set forth in detail in his Declaration, were of a nature, i.e. blinded randomized sites, specific and unambiguous rating scale, highly experienced and trained investigator and the like, that would render the data and results to be highly accurate and reliable. The test procedure is explained in specific detail in these Declarations and clearly shows that a miconazole nitrate/zinc oxide combination is both synergistic and efficacious at a ratio of 1:60 against Candida albicans.

We are also submitting herewith the Declaration of Dr. David Isaacson, one of the inventors of this application, who has done additional testing utilizing the procedures set forth in Example VII, pps. 10-12 of the specification for miconazole nitrate/zinc oxide combinations at 1:60 against Staphylococcus aureus. The results shown in this Declaration clearly demonstrate the synergistic nature against Staphylococcus aureus of the miconazole nitrate-zinc oxide combination at a ratio of about 1:60.

It is respectfully contended that the claims as amended find adequate support in the specification and find additional adequate experimental support in the Declarations Under Rule 132 submitted herewith. Accordingly, Applicants respectfully contend that the claims are allowable both as to form and over the prior art and therefore a reconsideration of the claims and a Notice of Allowance are respectfully requested.

Respectfully submitted,



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